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Transcranial Doppler Enhanced Thrombolysis for Embolic Occlusion of Major Cerebral Arteries

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Summary

For the treatment of 11 patients with hyperacute embolic occlusion of major cerebral arteries (ten with occlusion of middle cerebral artery and one with occlusion of basilar artery), TCD-enhanced thrombolysis (TCDET) was performed in combination with ultrasound irradiation, using diagnostic transcranial Doppler (TCD) (TC2-64B: 2MHz, 100mW/cm², pulsed wave) (TCDET group), and the effectiveness of this procedure was compared with that of local intra-arterial fibrinolysis (LIF) in 45 patients with embolic occlusion of the middle cerebral artery (LIF group). Regarding dose of TPA, the LIF group used 1046.7 ± 607.8 units and the TCDET group 700.0 ± 431.3 units ($p < 0.05$). Regarding time technically required to attain recanalization, the LIF group required 68.2 minutes, and the TCDET group 28.6 minutes. A good outcome was noted in 60.8% of the LIF group and 64% of the TCDET group. Haemorrhagic transformation was observed in 7.8% of the LIF group and in 0% of the TCDET group. No complications due to TCD irradiation were observed in the TCDET group. These findings suggest that TCDET can be an effective method of achieving recanalization.

Introduction

It has already become clear that in the treatment of hyperacute embolic occlusion of major cerebral arteries, local intra-arterial fibrinolysis (LIF) is more effective than drip infusion of 60,000 units/day of urokinase (UK), the only drug now permitted for this disease [1,2]. Although the rate of recanalization with LIF is high, it is necessary to make the indications for LIF more specific to avoid related postoperative haemorrhagic transformation. At present, diagnosis by MRI-DWI of the presence or absence of irreversible changes of brain and evaluation of remaining cerebral blood flow by dynamic CT and SPECT are considered effective. While it is desirable to specify the indications for LIF more precisely, few reports are available concerning reduction of the time technically required to attain recanalization so as to broaden the therapeutic time window. We therefore paid particular attention to the thrombolytic effects of ultrasound [3,4,5], and made an attempt to determine whether the use of LIF in combination with delivery of ultrasound irradiation to thrombi is effective in accelerating destruction of emboli and in reducing the time technically required to attain recanalization.

Material and Methods

In this study, 45 patients (males 32; females 13; ages 48-85 years with an average of 70.8 years) with embolic occlusion of the middle cerebral artery (MCA) who underwent LIF in our department between 1992 and 2001 were used as controls. For 11 patients (ten with oc-

clusion of MCA and one with occlusion of basilar artery; males, ten; female, one; ages, 63-84 years, with an average of 73.4 years) who underwent TCD-enhanced intra-arterial thrombolysis (TCDET), comparison was made with the control regarding the dose of fibrinolytic agent, time technically required from initiation of treatment to attaining recanalization, one-month outcome, and haemorrhagic transformation.

The indications were as follows: Those who came to the hospital within six hours of the onset of disease, and in whom no early CT signs of infarction were observed. For those who clearly presented nidus symptoms, dynamic CT was performed, following CT, to evaluate remaining cerebral blood flow, and when the ratio of peak value against the healthy side (L/N ratio) was 30% or more, LIF was performed following cerebral angiography.

Alteplase was used as a fibrinolytic agent. With a maximal dose set at 24 million units, one million units were dissolved in 10 ml of physiological saline, and the solution thus prepared was continuously injected as a bolus. Administration was discontinued when recanalization was confirmed.

The procedure for TCDET was exactly the same as for LIF alone. A 6F guiding catheter was placed in the target vessel, and Turbo-Tracker 18 or Microsoft Stream (each made by Boston) was deployed at a site where the tip of the catheter touched the peripheral end of the occluded lesion, or in the case of a catheter with a hole in its side, at a site where the side-hole touched the embolus. In addition, a diagnostic transcranial Doppler apparatus (TCD, TC2-64B:2MHz, PW, 100mW/cm^2) was setted at the temporal bone window. Continuous irradiation was performed, with depth set using, the sound of physiological saline being injected via the infusion catheter as a guide. In addition, real-time diagnosis of recanalization was performed.

Results

Dose of Fibrinolytic Agents

The dose of TPA was 10.467 ± 6.078 million units in the LIF group, and 7.000 ± 4.313 million units ($p < 0.05$) in the TCDET group. Thus, the dose of fibrinolytic agent used was significantly smaller in the TCDET group.

Recanalization Time

From the start of local placement of the microcatheter and fibrinolytic therapy to confirmation of recanalization, 68.2 ± 15.0 minutes was required in the LIF group, and 28.6 ± 17.5 minutes in the TCDET group. The time technically required to attain recanalization was thus decreased by half in the TCDET group.

Outcome

If, in determining one-month outcome, good recovery and moderate disability based on the Glasgow Outcome Scale are rated "good", and others "poor", the outcome in the LIF group was "good" in 60.8% of cases.

For the TCDET group, the rating was "good" in 64% of the cases. The rating was slightly better in the TCDET group, although not to a significant extent.

There were more cases of "poor" outcome in the TCDET group. This was partly due to the inclusion of two high-risk cases complicated by diabetes mellitus and renal failure, and partly because there was one case of complete calcification of emboli, which entirely neutralized the effect of ultrasound.

Haemorrhagic Complications

In the LIF group, symptoms of haemorrhagic transformation were observed in 7.8% of patients. In TCDET group, on the other hand, no such symptoms were observed.

No complications due to TCD irradiation were observed.

Discussion

The effectiveness of LIF for MCA occlusion has been demonstrated in many reports[1,2]. On the other hand, the main factor that makes the outcome poor is haemorrhagic transformation (HT). To avoid HT, the indications for LIF are presence or absence of reversible change of cerebral ischemia determined by MRI-DWI[6], dynamic CT and SPECT, or results of evaluation large extent of remaining cerebral blood flow. These measures make it possible to a large extent to avoid HT. As a result, the safety of LIF has been enhanced.

Meanwhile, in order to expand the indications for LIF, several measures have been tak-

en, such as measures for brain protection to widen the therapeutic time window, and ways to reduce the time technically required to achieve recanalization. However, few have been successful except for Edaravone, a drug which is claimed to have a brain-protecting effect, and which was quite recently put on the market. Its efficacy in protect of dilation of cerebral infarcts is expected.

Therefore, with the exception of direct PTA[7,8], measures to reduce the time technically required to attain recanalization seem to have reached their limits.

If something is to be selected that accelerates thrombolysis, and that is easy to use and safe, ultrasound can be considered to have the greatest likelihood of success. Because of its effect of cavitation and of elevating local temperature, high-output ultrasound has experimentally the ability to break up thrombi, and when used in combination with a fibrinolytic agent, its thromolytic effect is clearly enhanced. On the other hand, because of its high output, complications such as hemolysis, damage to vascular intima, and disorder of bone marrow frequently occur. Thus, some clinical problems remain, and ultrasound has yet to come to practical use[3-5].

However, we believe that the time required for recanalization can be reduced by TCD, which is frequently used for diagnostic purpose, when it is used for monitoring of recanalization in local intra-arterial fibrinolysis.

On the assumption that even low-output ultrasound may break up thrombi, we applied diagnostic TCD irradiation to emboli simultaneously with local administration of a fibrinolytic agent in LIF, for real-time diagnosis of recanalization and to evaluate thrombolysis. Then, comparison was made with treatment by LIF alone mainly regarding dose of fibrinolytic agent and time technically required to attain recanalization. Dose of fibrinolytic agent was decreased by 35%, and the time required for recanalization was shortened by half. Furthermore, there was some increase in frequency of "good" outcome, and no HT was observed.

The above results indicate that irradiation to thrombi even with a low-output ultrasonography apparatus can yield sufficient thrombolytic effect if used in combination with local administration of a fibrinolytic agent.

TCDET uses ultrasound of such output as is used generally in daily medical treatment, and such complications as observed in experimental high-output ultrasound have not been observed at all. Thus, no safety problems have been observed. However, if a fibrinolytic agent is given concomitantly through systemic intravenous route, is it possible to obtain a similar effect?

For systemic administration, it is impossible to perform this procedure unless correct diagnosis of the occluded site is made by cerebral angiography. Besides, it is unclear when recanalization was achieved after administration. Furthermore, in order to attain increased concentration of fibrinolytic agent in the occluded site, a large dose is necessary. This runs counter to the idea of reducing the dose of fibrinolytic agent.

In determining the TCD irradiation site and depth in LIF, the sound of drug injection through an infusion catheter placed in the embolus site works as a marker. For systemic administration, however, even in combination with TCD irradiation, it is difficult to deliver pinpoint irradiation to the area with no blood flow, because of the absence of blood flow sig-

Table 1 **Comparison of TPA dose, time technically required from initiation of treatment to attaining recanalization and one month prognopsis between local-intraarterial fibrinolysis and ultrasound enhanced local fibrinolysis**

	TPA dose (x 10,000 IU)	Recanalization time (min.)	Prognosis		H.T.
			GR and MD	SD and Dead	
LIF group	1046.7 ± 607.8	68.2 ± 15.0	60.8%	19.6%	7.8%
TCDET group	700 ± 431.3	26.3 ± 17.5	64%	36%	0%
	p < 0.05				

TPA: tissue plasminogen activator; GR: good recovery; MD: moderate disability; SD: severe disability (Glasgow Outcome Scale) H.T.: haemorrhagic transformation; LIF: local intra-arterial fibrinolysis; TCDET: transcranial Doppler enhanced intra-arterial thrombolysis

nal. Thus, combined use of ultrasound irradiation cannot be expected to be efficacious.

The above considerations indicate that it is difficult to use TCD concomitantly in systemic administration. Some researchers maintain that systemic administration of a fibrinolytic agent in combination with TCD irradiation to emboli was effective[9], but this is questionable.

The present maximum TCD output is 100mW/cm^2 for diagnostic purposes. The challenge now confronting us is how to increase this output or therapeutic purposes to 240mW/cm^2, the upper limit of the safety margin set by The Japan Society of Ultrasonics in Medicine, while maintaining safety. Effort in this respect will be important from the standpoint of reducing the time required for thrombolysis.

When this problem has been solved, and the indications for LIF should be expanded, and the scope of treatment of LIF will be widened.

Conclusions

With use of LIF for embolic occlusion of major cerebral arteries in combination with irradiation of ultrasound, it will become possible to decrease the dose of fibrinolytic agents and to reduce the time technically required to achieve recanalization.

It will also become possible to expand the indications for LIF.

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